Systematic Review

Radiofrequency Therapies for Trigeminal Neuralgia: A Systematic Review and Updated Meta-analysis

Xiaoyu Zhang, MSc, Lihua Peng, PhD, and Danyan Liu, PhD

From: Department of Anesthesiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Address Correspondence: Danyan Liu, PhD Department of Anesthesiology, The First Affiliated Hospital of Chongqing Medical University Chongqing, China. E-mail: Liudanyan418@qq.com; songsmind@163.com

Disclaimer: This study was supported by Chongqing Yuzhong District Science and Technology Project, China (20160116).

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 03-15-2022
Revised manuscript received: 08-28-2022
Accepted for publication: 10-10-2022

Free full manuscript: www.painphysicianjournal.com

Background: Conventional radiofrequency (CRF), pulsed radiofrequency (PRF), and pulsed combined conventional radiofrequency (PCRF) are widely used in the clinical treatment of trigeminal neuralgia (TN), collective evidence comparing the efficacy and safety of these radiofrequency therapies is still controversial.

Objectives: To provide additional evidence for the efficacy and safety of different radiofrequency therapies in the management of TN to update this section of the sys-tematic review of Wu et al 2019.

Study Design: A secondary systematic review and meta-analysis was conducted.

Methods: Systematic database research about double-blind, randomized controlled trials (RCTs) was conducted based on PubMed, Embase, and Web of Science. Literature on TN in adults under different radiofrequency therapies was collected to evaluate pain scores, excellent pain relief, and occurrence of adverse effects after corresponding therapies.

Results: A total of 11 studies, including 570 patients, were involved in our systematic review. Two studies from the same research team and one study with a completely different pain assessment tool were excluded from the meta-analysis. Ultimately, 8 studies, including 412 samples, were included in the quantitative synthesis. In secondary analyses, as with the report of Wu and colleagues, we also observed a safer outcome in PRF than CRF when regarding the occurrence of adverse effects. Nevertheless, unlike the last meta-analysis, despite no statistical difference in pain scores between CRF and PRF one week after surgery, a positive impact was observed in the CRF group one month and 3 months after surgery. A meta-analysis of 6 studies comparing PCRF and CRF was conducted and revealed no evidence to prove excellent pain relief of PCRF and CRF groups at 6 months, one year, and 2 years after surgery. However, a positive influence in reducing pain scores was observed in the PCRF group. Subgroup analysis further exhibited that PCRF positively affected TN when the temperature was lower than 70°C.

Limitations: (1) A small overall sample of included trials; (2) the diversity of tools used for pain assessment across trials, such as VAS, BNI, and NRS, limits the evaluation of outcomes; (3) a high risk exists for most studies in the meta-analysis for at least one domain, which may affect the reliability of results; (4) the short follow-up period of a few studies in the meta-analysis while the long-term efficacy of different radiofrequency treatments may require longer follow-up data to enhance the accuracy of the assessment.

Conclusions: PCRF provides better long-term efficacy and fewer adverse effects for treating TN. Yet, it is hard to draw definitive conclusions about excellent pain relief comparisons due to the moderate quality of evidence, high heterogeneity, and scarcity of available data.

Key words: Radiofrequency therapy, trigeminal neuralgia, systematic review, meta-analysis

Pain Physician 2022: 25:E1327-E1337

Trigeminal neuralgia (TN) is a unilaterally paroxysmal neuropathic pain characterized as recurrent, sudden, touch-triggered, and tingling pain within one or more divisions of the trigeminal nerve (1). Although each pain attack only lasts for a short period, the paroxysm is unbearable due to its recurrence and electric shock-like perception, leading to disability or depression in severe cases (2). Accordingly, it is challenging to find a way to cure trigeminal neuropathic pain completely.

The radiofrequency ablation procedure is one of the most prominent minimally invasive therapies for TN, with the analgesia mechanism relevant to radiofrequency thermal coagulation of the trigeminal ganglia (3,4). Specifically, conventional radiofrequency (CRF) produces high temperatures to selectively destroy nerves using a high-frequency current. The thermal coagulation temperature of CRF is set at 60-75°C and cycles 60 seconds with sensory disorders occurring simultaneously with pain relief (5,6). Pulsed radiofrequency (PRF) produces an analgesic effect on the nerve tissue with the intermittent issuance of pulsed current at 42°C to reduce tissue destruction (7,8). Previous studies have reported that CRF has better efficacy than PRF in managing TN. However, since CRF causes frequent adverse effects (9), a growing number of studies are focusing on the pulsed combined conventional radiofrequency (PCRF) technique, which is based on the rationale of enhancing the effectiveness of CRF treatment and reducing the side effects produced by its prolonged action on tissues by utilizing the respective advantages of CRF and PRF (10-12). Yet, the patterns of radiofrequency and stimulation parameters differ across studies.

A previous systematic review and meta-analysis by Wu and colleagues has indicated the benefits of PCRF for patients with TN but included data for ambiguous time points and was insufficient to draw determinate conclusions (13). Also, the prior meta-analysis conducted and pooled some data from the same research team, further creating uncertainty in the conclusions. Additionally, all pooled data were calculated using the odds ratio (OR), and the high heterogeneity test was discounted, perhaps leading to poor accuracy and comprehensiveness of the analysis.

For the past 3 years, some new randomized controlled trials (RCTs) on different radiofrequency therapies treating TN have been published, providing additional evidence for the use of radiofrequency treatments for patients with TN. Thus, here we sought to update the prior meta-analysis and further determine the efficacy and safety of the treatment of TN in different radiofrequency conditions.

Methods

This meta-analysis protocol abided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (14) and registered in the International Prospective Register of Systematic Reviews (PROSPERO) within the number CRD42022309398.

Search Strategy

Studies published from January 2005 to December 2021 about double-blind RCTs associated with CRF or PRF as advanced analgesia in patients with TN were searched using PubMed, Embase, and Web of Science. For a comprehensive search of the intended literature, we retrieved the subject terms including TN, radiofrequency therapy, RCT, and free words pertinent to MeSH terms within PubMed, to design a search strategy that can be found in Appendix 1.

Eligibility Criteria

Studies were integrated into the eligibility assessment considering the following criteria: (a) Studies are RCTs and prospective observational trials; (b) Participants are patients with trigeminal neuropathic pain; (c) Initial RCTs compare the efficacy and safety of different radiofrequency therapies in relieving TN; (d) Full text of the studies are reported in the English language.

Study Selection

Two reviewers imported the literature into EndNote in accordance with the previous full search strategy, independently glanced over the relevant records, and removed duplicates. After eliminating parts of the records based on the titles and abstracts, full-text articles were screened and assessed for eligibility to exclude articles about animal experiments, case reports, meeting abstracts, and non-RCTs. A third reviewer made the final judgment when 2 reviewers disagreed on excluding a study.

Data Extraction

Data were extracted from the relevant literature by the 2 reviewers independently, including authors, publication year, type of study, mean age of the sample, diagnosis, intervention, sample size, follow-up duration, pain outcomes (pain scores and excellent pain relief), and adverse effects. A third reviewer made the final judgment when any disagreement occurred between the 2 reviewers.

Risk of Bias Evaluation

The risk of bias in the included RCTs was assessed by the 2 reviewers independently, using the Cochrane risk-of-bias tool in the RevMan software (15). A third reviewer made the final judgment when any disagreement occurred between the 2 reviewers.

Seven items were embodied in the risk of bias tool: (a) random sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessment, (e) incomplete outcome data, (f) selective reporting, and (g) other bias. Each item was divided into low risk, unclear risk, and high risk to indicate the quality of evidence.

Statistical Analysis

As secondary analyses, our interested primary outcomes, including excellent pain relief, pain scores, and side effects occurrence, were analyzed after collecting. The World Health Organization's evaluation criteria for pain relief was used to estimate excellent pain relief, which means a complete resolution of pain with no medication. Pain scores were measured by various scales, including the Visual Analog Scale (VAS) and the Numeric Rating Scale (NRS), ranging from 0 to 10 points. The lowest point of the scale implies no pain, and the highest point corresponds to unbearable pain. The adverse effect outcomes primarily encompass facial numbness, masticatory muscle weakness, and dysesthesia. In this study, the relative risk (RR) in excellent pain relief rate and complication rate was calculated with its 95% confidence interval (CI). The weighted mean difference (MD) was used for pain scores at numerous time points after radiofrequency therapy. The standard mean difference (SMD) for the continuous and dichotomous variable of the VAS scale was calculated according to the Cochrane Handbook (16). I^2 statistic was used for heterogeneity test, and random-effects models were applied when $I^2 > 50\%$ (17). Additionally, the complication rates of subgroups were compared based on the different temperatures. A sensitivity analysis was conducted using a case-by-case exclusion method. All analyses were performed using Review Manager (RevMan) Version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark).

Results

Literature Selection

A total of 90 articles relevant to CRF, PRF, or PCRF treating patients with TN were retrieved through the database searching from January 2005 to December 2021. After 17 duplicates were removed, 34 records were also eliminated by screening the titles and abstracts. Then, 39 full-text articles were left to be assessed for eligibility, and 28 records were excluded for various reasons. Finally, a total of 11 studies were included in the quantitative synthesis. The article selection process is presented in Fig. 1 (9,10,18-26).

Study Characteristics

A total of 11 studies were included in the systematic review, and the detailed characteristics are listed in Table 1. Except for 2 other papers published in 2007 and 2012, most were issued between 2015 and 2021. The range of follow-up duration of included trials was 6 months, one year, 2 years, and even 5 years. A total of 625 patients participated in the initial studies, but only 570 patients completed the follow-up, while others were disconnected due to unreachable phone calls or death.

Each study included in the systematic review was an RCT related to different types of TN. In all included trials, 3 studies compared the CRF and PRF therapies (9,19,20), 6 studies compared PCRF and CRF (10,18,20,22,24,25), and 2 studies compared CRF at different temperatures (23,25). A high-voltage PRF versus standard-voltage PRF could not

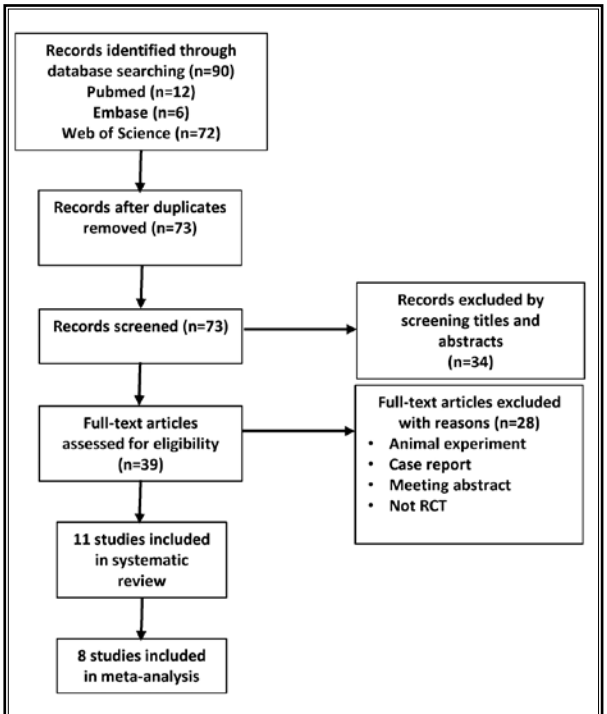

Fig. 1. *PRISMA flow chart of literature selection.*

Table 1. *Characteristics of the included studies relevant to radiofrequency therapy treating TN.*

Author, Year	Type of study	Age (Mean ± SD)	Diagnosis (type of trigeminal neuralgia)	Division of the trigeminal nerve, n	Intervention	Temperature setting	Sample, n	Follow-up duration	Main Outcomes	Key Findings
Abdel-Rahman et at, 2020	RCT	55.67 ± 8.40 y	Recurrent trigeminal neuralgia	V2, 5 V3, 9 V2 +V3, 18 V1 + V2 + V3, 5	Combined pulsed and thermal radiofrequency vs. thermal Radiofrequency	42°C PRF+60°C RF vs 70°C RF	n = 40 n = 37 completed follow-up duration	At hospital Discharge, 6, 12, 18, and 24 months	Barrow Neurological Institute Pain Intensity (BNI) Scale; Overall complications	(-) $P < 0.05$
Agarwal et al, 2021	RCT	54.91 ± 10.30 y	Idiopathic trigeminal neuralgia	V1, 1 V2, 5 V3, 3 V1 + V2, 6 V2 +V3, 8 V1 + V2 + V3, 1	Conventional radiofrequency vs. pulsed radiofrequency	70°C CRF vs. 42°C PRF	n = 27 n = 24 completed follow-up duration	At 7 days, 1, 2, 3, and 6 months	Visual Analog Scale (VAS); BNI score; Mild hyposethesia	$P < 0.05$ at 1, 2, 3, 6, mon $P < 0.05$ at 3, 6 mon $P < 0.05$
Ding et al, 2018	RCT	56.12 ± 9.94 y	V2/V3 Primary trigeminal neuralgia	V2, 23 V3, 27 V2 + V3, 30	Pulsed radiofrequency combined with low-temperature continuous radiofrequency vs continuous radiofrequency	42°C PRF + 68°C CRF vs 68°C CRF	n = 80; n = 80 completed follow-up duration	At the first day, 7 days, 1, 3, 6, 12, and 24 months	VAS score; Degree of Pain Relief; Facial numbness; Weakness of masticatory muscles; Weakened corneal reflex; Recovery time for side effects	$P < 0.05$ at 1, 3, 6, 12, 24 mon $P < 0.05$ at 6, 12, 247 y (-) (-) (-) $P < 0.05$
Elawamy et al, 2017	RCT	53.80 ± 10.06 y	Idiopathic trigeminal neuralgia	V2, 2 V3, 3 V2 +V3, 36 V1 + V2 + V3, 3	Continuous radiofrequency vs. pulsed radiofrequency vs. combined continuous and pulsed radiofrequency	42°C PRF vs 75°C CRF vs 42°C PRF + 60°C CRF	n = 60; n = 43 completed follow-up duration	At baseline, 7 days, 1, 6, 12, and 24 months	VAS score; Patient satisfaction; Excellent pain relief rate; Weakness of muscles of mastication	$P < 0.01$ at 12, 24 mon $P < 0.05$ at 1, 6 mon $P < 0.01$ at 6, 12, 24 mon (-)
Fang et al, 2015	RCT	62.00 ± 12.47 y	Idiopathic trigeminal neuralgia	V2, 6 V3, 23 V2+V3,31	High-voltage Pulsed Radiofrequency vs. Standard-voltage Pulsed Radiofrequency		n = 60; n = 60 completed follow-up duration	At the first day, 7 days, 14 days, 1, 3, 6, and 12 months	Numeric Rating Scales (NRS); Effective rates	$P < 0.05$ at 3, 6 mon $P < 0.05$ at 1, 3, 6, 12 mon
Erdine et al, 2007	RCT	62.15 ± 12.02 y	Idiopathic trigeminal neuralgia		Pulsed radiofrequency vs. conventional radiofrequency	70°C CRF vs. 42°C PRF	n = 40; n = 40 completed follow-up duration	At the first day, 3, and 6 months	VAS score; Patient satisfaction (PSS); Mild hypoesthesia; Paresthesia	$P < 0.01$ $P < 0.01$ $P < 0.05$ $P < 0.05$
Li et al, 2012	RCT	56.68 ± 10.17 y	Classic trigeminal neuralgia	V2, 16 V3, 22 V2 + V3, 22	Pulsed radiofrequency combined with continuous radiofrequency vs. continuous radiofrequency	42°C PRF + 75°C CRF vs. 75°C CRF	n = 60; n = 58 completed follow-up duration	At the baseline, 1, 3, 7 days, 3, 6, and 12 months	Pain relief rate; NRS score; Quality of life (QOL); Intensity of facial dysesthesia; Masticating function weakness	(-) $P < 0.05$ (-) $P < 0.05$ $P < 0.05$

Table 1 (continued). *Characteristics of the included studies relevant to radiofrequency therapy treating TN.*

Author, Year	Type of study	Age (Mean ± SD)	Diagnosis (type of trigeminal neuralgia)	Division of the trigeminal nerve, n	Intervention	Temperature setting	Sample, n	Follow-up duration	Main Outcomes	Key Findings
Yao et al, 2016	RCT	55.85 ± 11.34 y	V1 trigeminal neuralgia	V1, 56	Continuous radiofrequency thermocoagulation plus pulsed radiofrequency vs. continuous radiofrequency	42°C PRF + 62°C CRF VS 62°C CRF	n = 56; n = 50 completed follow-up duration	At 1-6 months (once per month), 12, 24, and 36 months	Health-related quality of life (HRQoL); SF-36 score; Facial numbness; Recovery time	$P < 0.05$ $P < 0.05$ at 24, 36 mon $P < 0.05$ $P < 0.05$
Luo et al, 2017	RCT	63.00 ± 13.08 y	V2 trigeminal nerve	V2, 60	High-voltage Pulsed Radiofrequency vs Standard-voltage Pulsed Radiofrequency		n = 60; n = 42 completed follow-up duration	At 1, 3, 6, and 12 months	NRS decrease >50%; Severe numbness	$P < 0.05$ at 1, 3, 6, 12, mon (-)
Zhao et al, 2015	RCT	59.3 y (38-81)	Primary trigeminal neuralgia		Radiofrequency thermocoagulation combined with pulsed radiofrequency vs. continuous radiofrequency	42°C PRF + 70°C CRF vs 70°C CRF	n = 80; n = 80 completed follow-up duration	At the baseline, 1, 7, 14 days, 1, 3, 6 months	Effect of time on complications; Masticatory muscles weakness; Decrease in corneal reflex	$P < 0.05$ at 6 mon $P < 0.05$ at 6 mon $P < 0.05$
Yao et al, 2016	RCT	53.20 ± 11.30 y	Bilateral idiopathic trigeminal neuralgia	V2, 14 V3, 23 V2 + V3, 25	Radiofrequency thermocoagulation at 68°C vs. radiofrequency thermocoagulation at 75°C	68°C RF vs. 75°C RF	n = 62; n = 56 completed follow-up duration	once per month within the first 6 months, once every 3 months within 4.5 years	Pain relief rate; Recurrence rate; Patient satisfaction; Facial numbness; Corneal hypoesthesia Masticatory atonia	(-) (-) $P < 0.05$ $P < 0.05$ $P < 0.05$

(-) No statistically significant difference between groups. $P<0.05$, $P<0.01$ means statistically significant difference between groups. BNI=Barrow Neurological Institute Pain Intensity; VAS=Visual Analog Scale; NRS=Numeric Rating Scales; PSS=patient satisfaction; QOL=score and quality of life; HRQoL=Health-related quality of life;

be performed in meta-analysis as the 2 studies were from the same research team (21,26). Furthermore, a meta-analysis of radiofrequency treatment at different temperatures (23,25) could not be conducted due to no extractable outcomes of interest in these 2 studies. Ultimately, 8 studies, including 412 samples, were included in the quantitative synthesis. Four studies evaluated the pain relief efficiency using Barrow Neurological Institute (BNI) pain intensity scale. One study used BNI < I (24) as an effective result, while the 3 others used BIN < III (18,19,23). Additionally, the primary outcomes of interest, such as the excellent pain relief and VAS pain scores were used in 4 trials. Most of the complications reported in included studies were facial numbness, masticatory muscle weakness, and dysesthesia.

Risk of Bias in Studies

The risk of bias assessment for included studies is shown in Figs. 2 and 3. All of the 11 studies had an unknown level of bias in multiple terms, with most studies evaluated to have a high risk of bias in at least one term. Specifically, the high risk of bias in the outcome domains was present in 3 studies because the outcome assessors of the 3 RCTs were aware of the implementation of interventions. In addition, 4 studies were evaluated to have a high risk of bias for selective reporting measurement because lack of objectivity in pain assessment, which could bias the outcome indicators toward statistical differences.

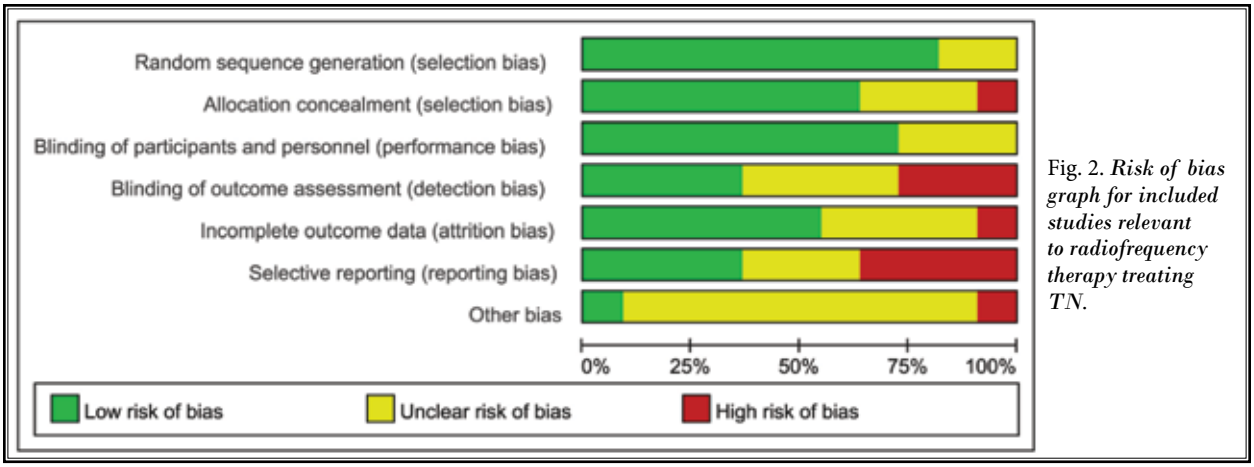

Fig. 2. *Risk of bias graph for included studies relevant to radiofrequency therapy treating TN.*

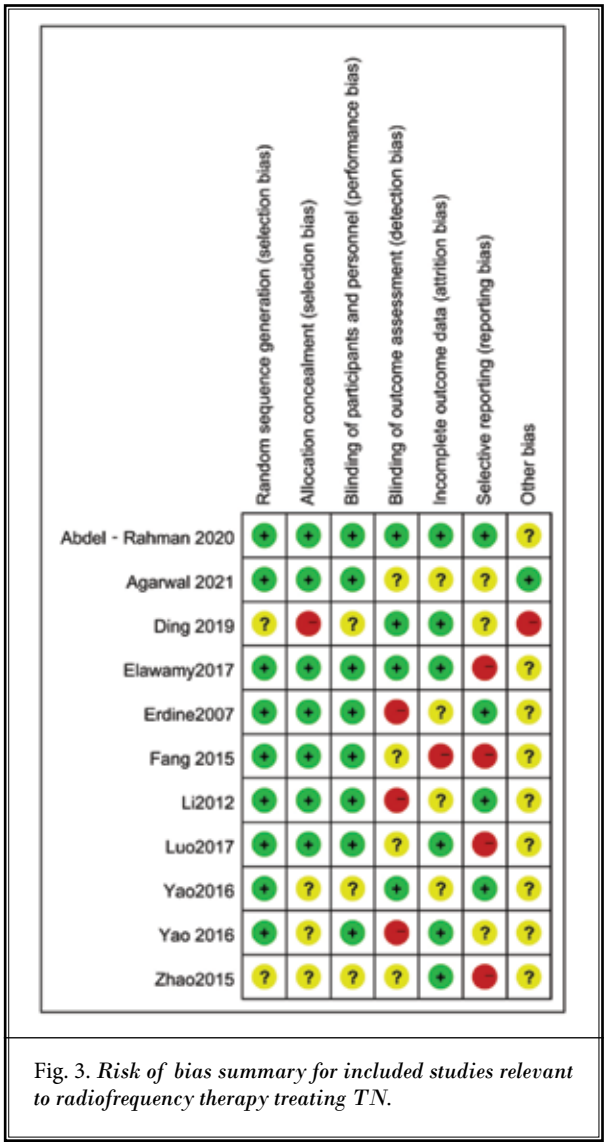

Fig. 3. *Risk of bias summary for included studies relevant to radiofrequency therapy treating TN.*

Meta-Analysis

Primary Outcomes in Comparison of Conventional Radiofrequency and Pulsed Radiofrequency

A total of 3 studies on the comparison of CRF and PRF treatments reported pain scores and adverse effects involving 107 patients. Two of 3 studies reported the VAS pain scores (9,20), while another one mentioned the population of decrease in VAS scores ≥ 50% (19). To facilitate meta-analysis, we extracted data from these trials at the same points and calculated SMD values after integrating continuous and dichotomous variables using the Cochrane handbook. The pooled results showed no statistical changes in pain score between CRF and PRF therapies at one week postoperatively (SMD -0.31; 95%CI = -1.38 to 0.76; I^2 = 83%, P = 0.01, Fig. 4A). At one month after surgery, the pain score of the CRF group was less than that of PRF (SMD -0.58; 95%CI = -0.79 to -0.37; I^2 = 5%, P = 0.3, Fig. 4B). A similar result was presented at 3 months postoperatively, indicating that CRF could cure trigeminal neuropathic pain more effectively than PRF (SMD -1.00; 95%CI = -1.98 to -0.01; I^2 = 86%, P = 0.008, Fig. 4C). Data of adverse effects were pooled in the meta-analysis, demonstrating that CRF also had a higher incidence of adverse reactions than PRF (RR 7.36; 95%CI = 1.07 to 50.84; I^2 = 54%, P = 0.12, Fig. 5).

Primary Outcomes in Comparison of Pulsed Combined Conventional Radiofrequency and Conventional Radiofrequency

The incidence of excellent pain relief after PCRF and CRF treatment was mentioned in 4 of 6 studies involving 231 patients (10,20,22,24). We pooled the

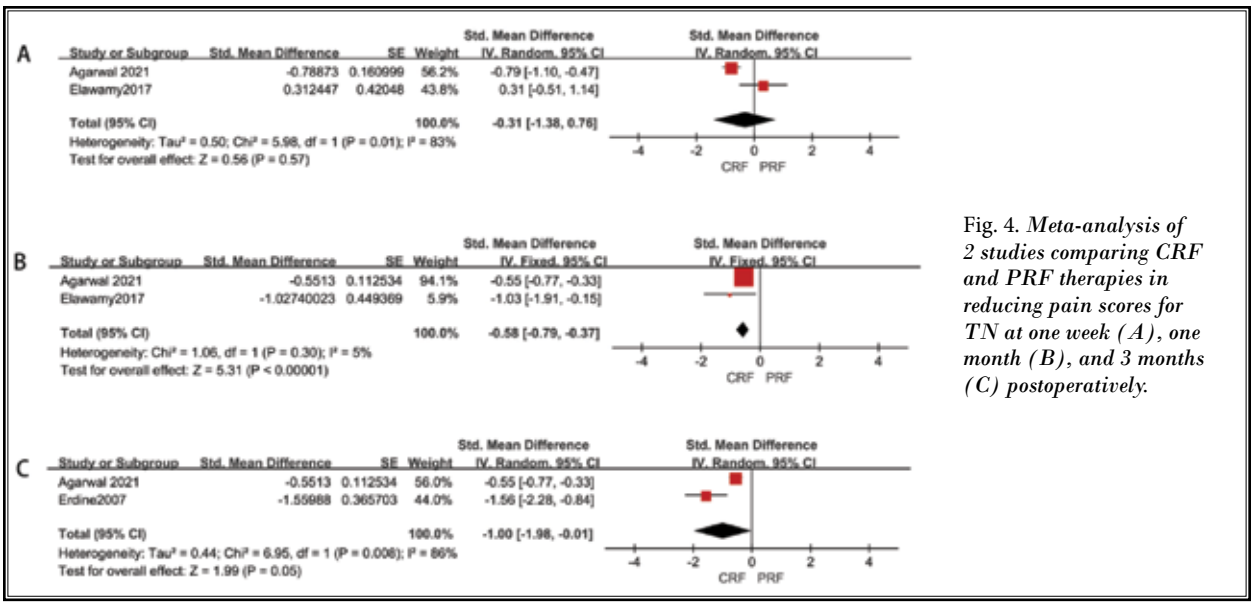

Fig. 4. *Meta-analysis of 2 studies comparing CRF and PRF therapies in reducing pain scores for TN at one week (A), one month (B), and 3 months (C) postoperatively.*

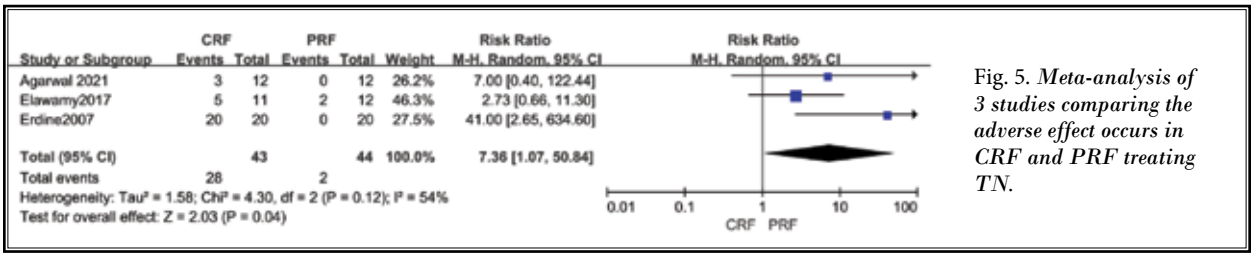

Fig. 5. *Meta-analysis of 3 studies comparing the adverse effect occurs in CRF and PRF treating TN.*

results at 6 months (RR 1.22; 95%CI = 0.83 to 1.79; I^2 = 72%, *P* = 0.03, Fig. 6A), one year (RR 1.30; 95%CI = 0.92 to 1.85; I^2 = 70%, *P* = 0.02, Fig. 6B), and 2 years (RR 1.55; 95%CI = 0.86 to 2.77; I^2 = 71%, *P* = 0.03, Fig. 6C) postoperatively into the meta-analysis and found no evidence could prove that the excellent pain relief in the PCRF group was better than that in the CRF group. Whereas a total of 2 studies on the comparison of PCRF and CRF treatments reported pain scores involving 123 patients. The results of pain scores at one year (MD -0.30; 95%CI = -0.43 to -0.17; I^2 = 0%, *P* = 0.34, Fig. 7A) and 2 years (MD -0.75; 95%CI = -0.91 to -0.59; I^2 = 49%, *P* = 0.16, Fig. 7B) after surgery (10,20) were included in the meta-analysis, showing that PCRF could better decrease the pain scores of patients with TN compared with CRF. Furthermore, the pooled results of adverse effect occurrence reported in 6 studies involving 348 patients (10,18,20,22,24,25) demonstrated that PCRF decreased the incidence of adverse effects compared with CRF treating TN (RR 0.58; 95%CI = 0.35 to 0.96; I^2 = 60%, *P* = 0.03, Fig. 8).

Sensitivity Analysis

A sensitivity analysis result from meta-analysis relevant to the comparison of various radiofrequency treatments showed robustness in adverse effect occurrence. Due to high heterogeneity in the excellent pain relief, sequential exclusion of individual studies finding that the study which originated from the study of Elawamy et al (20), led to the changes in meta-analysis results (Appendix Table 1).

Subgroup Analysis

Due to the temperature of PCRF being referenceable in treating patients with trigeminal neuropathic pain, a post hoc subgroup analysis of adverse reactions occurrence of patients with TN after PCRF treatment at different temperatures was conducted. The results exhibited that the temperature below 70°C had a positive effect on TN (RR 0.46; 95%CI = 0.22 to 0.96; I^2 = 42%, *P* = 0.16, Fig. 9). Whereas no statistical difference was observed in the 2 groups of temperatures higher than 70°C (RR 0.72; 95%CI = 0.38 to 1.38; I^2 = 76%, *P* = 0.04, Fig. 9).

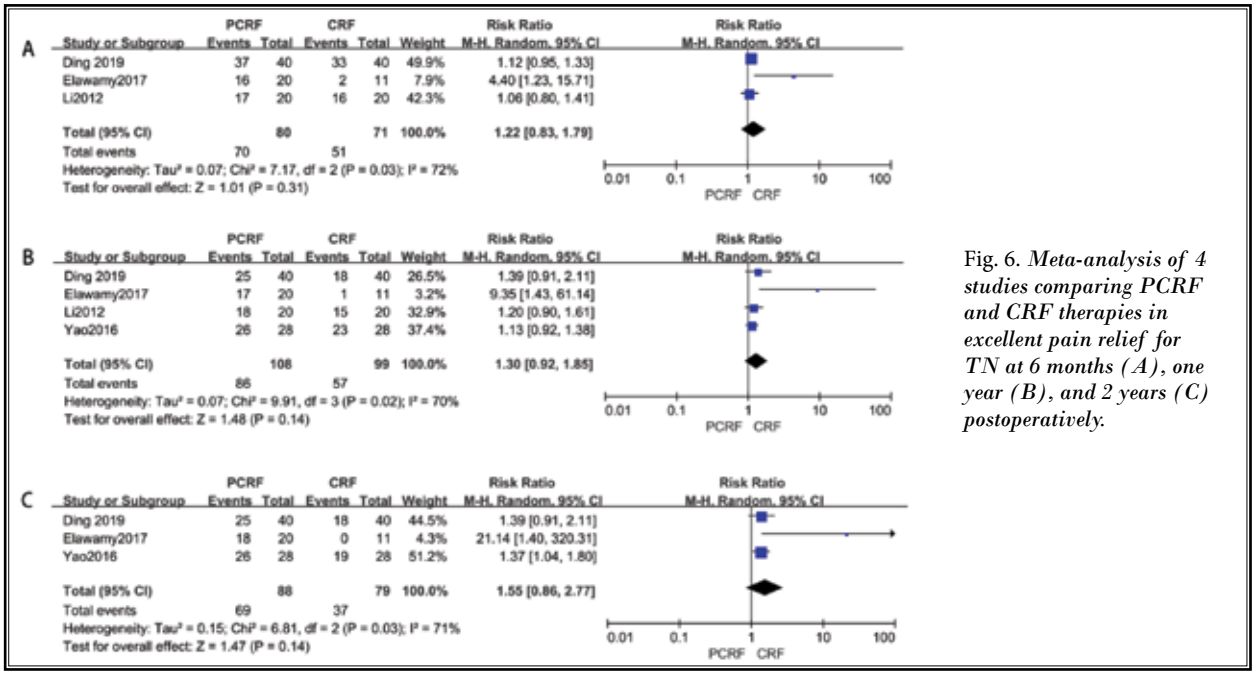

Fig. 6. *Meta-analysis of 4 studies comparing PCRF and CRF therapies in excellent pain relief for TN at 6 months (A), one year (B), and 2 years (C) postoperatively.*

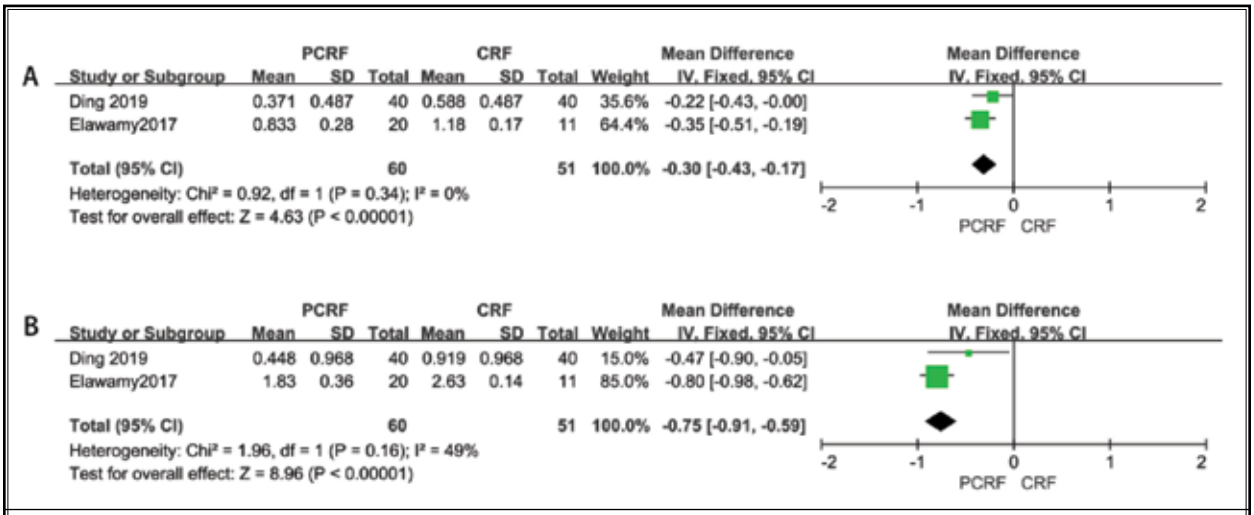

Fig. 7. *Meta-analysis of 2 studies comparing PCRF and CRF therapies in reducing pain scores for TN at one year (A), and 2 years (B) postoperatively.*

Discussion

Our systematic review was conducted to compare and verify the efficacy and safety of different radiofrequency therapies in relieving trigeminal neuropathic pain 3 years after the systematic review by Wu and colleagues reported on this topic (13). Briefly, this review yielded 11 trials and identified a total of 570 patients who com-pleted the follow-up, while only 8 of 11 studies were finally included. The other 3 studies were eliminated due to unignorable factors such as the data from the same research team or the unavailability of data of interest. The pooled results of this study substantiated and strengthened prior cardinal findings that PRF and PCRF were safer in managing patients with TN. However, as the apparent limitations of the previous systematic review, we confirmed that, although no difference was reported in the analysis of Wu et al (2019) about cure rate between CRF and PRF

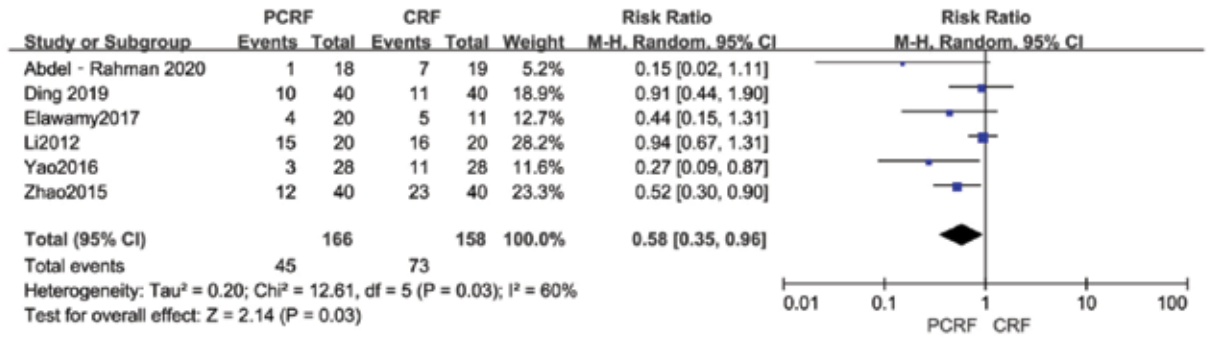

Fig. 8. *Meta-analysis of 6 studies comparing the adverse effect occurs in PCRF and CRF treating TN.*

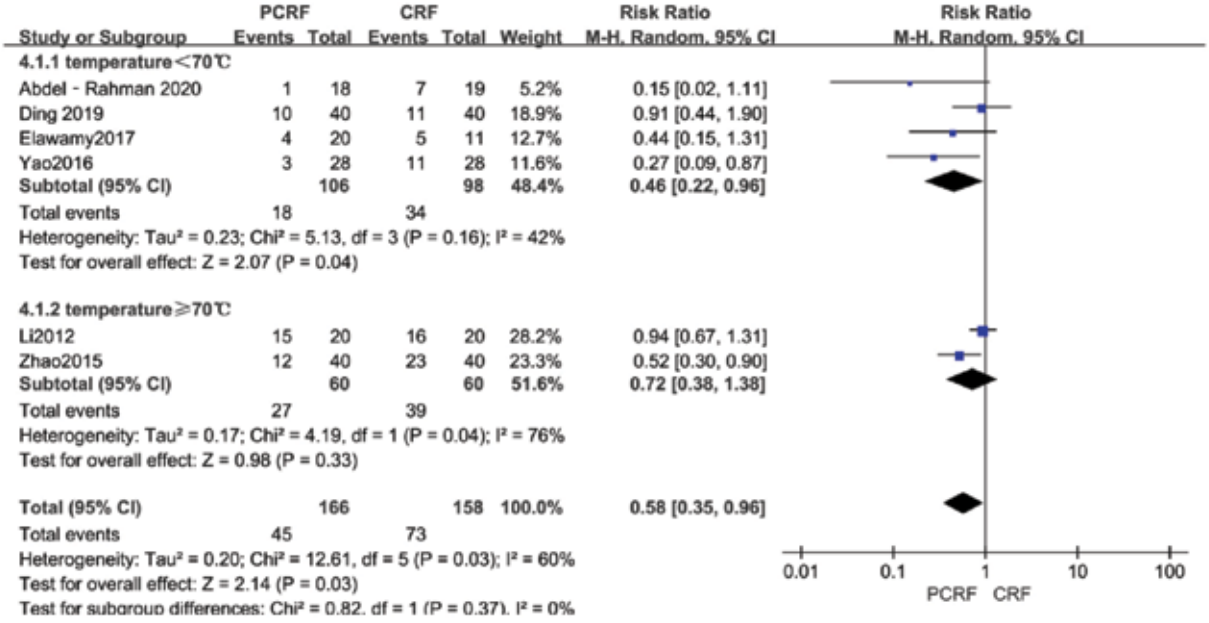

Fig. 9. *Subgroup analysis of adverse effect occurs at different temperatures of PCRF compared with CRF in treating TN.*

(13), pain scores of short-term in CRF were decreased obviously in secondary analyses, indicating a better efficacy indeed exists with CRF.

The mechanisms underlying TN have not been fully clarified. However, local hyperexcitability produced by demyelination of the trigeminal nerve roots may be a crucial link in the development of nociceptive hypersensitivity in the organism (27,28). Medication is generally the primary alternative in treating TN, of which long-term use may cause severe tolerance (29). Radiofrequency therapy is currently the most widely used intervention for trigeminal neuropathic pain other than medication. Radiofrequency emits a continuous current between 2 electrodes, which placed separately on the external surface of the body and at the tissue to be treated, to coagulate tissue thermally or produce a pulsed current to result in sensory abnormalities in the distribution of trigeminal nerve (3,30,31).

In secondary analyses, a meta-analysis of 3 studies comparing the pain scores and adverse effects occurrence of CRF and PRF revealed that CRF had better efficacy and poorer safety in providing analgesic effect on trigeminal neuropathic pain at 1-3 months postoperatively. The studies of Erdine et al (9) and Agarwal

et al (19) showed that the CRF technique had significantly lower VAS pain scores than PRF in the short term. However, data from Elawamy et al (20) showed that the superiority of CRF in decreasing trigeminal neuropathic pain was exhibited after at least 12 months. Additionally, since the methodology used by Agarwal et al (19) differed from the other studies in that it did not directly count VAS scores but used a reduction in VAS scores ≥ 50% to determine efficacy. Therefore, it is not easy to draw positive conclusions relevant to the comparison of CRF and PRF treatments using SMD to pool these data of trials in this review. Regarding the results about side reactions of different radiofrequency among included studies, CRF appears to be more prone to cause side reactions than PRF treatment.

Unlike the assessment of CRF and PRF in the short and intermediate term, we have collected a common postoperative 12-24 months outcome for both CRF and PCRF techniques in secondary analyses. Meta-analyses for comparing pain reduction and side effects of CRF and PCRF treatments on TN were conducted in 6 studies, indicating that no sufficient evidence could prove a better incidence of excellent pain relief in PCRF therapy. However, the results in studies of Ding et al (10), Elawamy et al (11), Li et al (22), and Yao et al (12) must be handled with caution due to their high heterogeneity. In this regard, the one-by-one sensitivity analysis showed a change in the 12-24 months outcomes after excluding the study of Elawamy et al (11). We observed that the data about excellent pain relief on the CRF group in the study of Elawamy et al (11) differed greatly from the other 3 studies. In addition, we reviewed the bias of risk assessment and found at least one poor quality entry in an individual study of 3 trials. Thus, conclusions relevant to excellent pain relief could not be hastily drawn. What is noteworthy is that 2 studies reported pain scores. When data on VAS scores over the 12-24 months period were analyzed, it was still possible to conclude a significant pain reduction of TN in the long term with PCRF. Interestingly, after reviewing the included trials, we found that effective long-term pain relief was able to be achieved with PRF at 42°C for 4 to 5 cycles of 120s followed by CRF at temperatures of 60°C-68°C for 180s to 270s, regardless of the subclassification of TN patients treated. Additionally, PCRF had remarkably fewer adverse reactions following the treatment of TN in the enrolled studies. Sensitivity analysis of side effects of various radiofrequency on TN revealed no change demonstrating a reliable result. The temperature used by radiofrequency ablation is critical to the clinical treatment of TN, especially the temperature of CRF, as it reduces pain through the thermal coagulation of tissue (32,33). However, Wu and colleagues conducted the subgroup analysis of safety between different temperatures in CRF treating TN based on 2 studies of the same team (23,34), perhaps leading to a multiple publication bias. In this regard, our secondary subgroup analysis avoided this risk and pooled results to further indicate that temperature below 70°C was safer in TN treatment via PCRF.

Limitations

Our study also has several limitations. First, although 11 studies were included in our review, only 8 RCTs with a small overall sample were ultimately quantified and analyzed. Second, the diversity of tools used for pain assessment across trials, such as VAS, BNI, and NRS, limits the evaluation of outcomes. Third, a high risk exists for most studies in the meta-analysis for at least one domain, which may affect the reliability of results. Fourth, the short follow-up period of a few studies in the meta-analysis, while the long-term efficacy of different radiofrequency treatments may require longer follow-up data to enhance the accuracy of the assessment.

Conclusion

This secondary systematic review and meta-analysis of different radiofrequency treatments in TN has remedied the lack of the previous meta-analysis that only counted data at one time point by comparing and pooling both short-term and long-term data, with sufficient evidence that PCRF provides better long-term efficacy and fewer adverse effects than CRF and PRF treatments. Furthermore, it may be safer for TN patients to receive 4 to 5 cycles of 120s at 42°C and then warm up to below 70°C for 180s to 270s of PCRF than to maintain a high temperature all the time. Nevertheless, it is hard to draw definitive conclusions about excellent pain relief comparisons due to the moderate quality of evidence, high heterogeneity, and scarcity of available data. Hence, more RCTs and samples are needed in the future.

Author Contributions

XZ and DL designed the protocol of study. Data extraction and analysis: XZ and LP. Drafting the manuscript: all authors. All authors have approved the final version.

References

1. Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G. Trigeminal neuralgia - diagnosis and treatment. *Cephalalgia* 2017; 37:648-657.
2. Zakrzewska JM, Wu J, Mon-Williams M, Phillips N, Pavitt S H. Evaluating the impact of trigeminal neuralgia. *Pain* 2017; 158:1166-1174.
3. Huang B, Xie K, Chen Y, Wu J, Yao M. Bipolar radiofrequency ablation of mandibular branch for refractory V3 trigeminal neuralgia. *J Pain Res* 2019; 12:1465-1474.
4. Lin H, Cao G, Jin G, et al. Extracranial non-gasserian ganglion application of radiofrequency thermocoagulation on the mandibular branch of the trigeminal through the foramen ovale for trigeminal neuralgia. *Pain Physician* 2021; 24:E425-E32.
5. Fields HL. Treatment of trigeminal neuralgia. *N Engl J Med* 1996; 334:1125-1126.
6. Nurmikko TJ, Eldridge PR. Trigeminal neuralgia--pathophysiology, diagnosis and current treatment. *Br J Anaesth* 2001; 87:117-132.
7. Bogduk N. Pulsed radiofrequency. *Pain Med* 2006; 7:396-407.
8. Cosman ER Jr, Cosman ER Sr. Electric and thermal field effects in tissue around radiofrequency electrodes. *Pain Med* 2005; 6:405-424.
9. Erdine S, Ozyalcin NS, Cimen A, Celik M, Talu GK, Disci R. Comparison of pulsed radiofrequency with conventional radiofrequency in the treatment of idiopathic trigeminal neuralgia. *Eur J Pain* 2007; 11:309-313.
10. Ding Y, Li H, Hong T, Zhu Y, Yao P, Zhou G. Combination of pulsed radiofrequency with continuous radiofrequency thermocoagulation at low temperature improves efficacy and safety in V2/V3 primary trigeminal neuralgia. *Pain Physician* 2018; 21:E545-E553.
11. Elawamy A, Abdalla EEM, Shehata GA. Effects of pulsed versus conventional versus combined radiofrequency for the treatment of trigeminal neuralgia: A prospective study. *Pain Physician* 2017; 20:E873-E881.
12. Yao P, Hong T, Zhu YQ, et al. Efficacy and safety of continuous radiofrequency thermocoagulation plus pulsed radiofrequency for treatment of V1 trigeminal neuralgia: A prospective cohort study. *Medicine (Baltimore)* 2016; 95:e5247.
13. Wu H, Zhou J, Chen J, Gu Y, Shi L, Ni H. Therapeutic efficacy and safety of radiofrequency ablation for the treatment of trigeminal neuralgia: A systematic review and meta-analysis. *J Pain Res* 2019; 12:423-441.
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; 62:e1-e34.
15. Higgins J P, Altman D G, Gøtzsche P C, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928.
16. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019; 10:ED000142.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21:1539-1558.
18. Abdel-Rahman KA, Elawamy AM, Mostafa MF, et al. Combined pulsed and thermal radiofrequency versus thermal radiofrequency alone in the treatment of recurrent trigeminal neuralgia after microvascular decompression: A double blinded comparative study. *Eur J Pain* 2020; 24:338-345.
19. Agarwal A, Rastogi S, Bansal M, Kumar S, Malviya D, Thacker AK. Radiofrequency treatment of idiopathic trigeminal neuralgia (conventional vs. pulsed): A prospective randomized control study. *Anesth Essays Res* 2021; 15:14-19.
20. Elawamy A, Abdalla EEM, Shehata GA. Effects of pulsed versus conventional versus combined radiofrequency for the treatment of trigeminal neuralgia: A prospective study. *Pain Physician* 2017; 20:E872-E881.
21. Fang L, Tao W, Jingjing L, Nan J. Comparison of high-voltage- with standard-voltage pulsed radiofrequency of gasserian ganglion in the treatment of idiopathic trigeminal neuralgia. *Pain Pract* 2015; 15:595-603.
22. Li X, Ni J, Yang L, et al. A prospective study of Gasserian ganglion pulsed radiofrequency combined with continuous radiofrequency for the treatment of trigeminal neuralgia. *J Clin Neurosci* 2012; 19:824-828.
23. Yao P, Hong T, Wang ZB, et al. Treatment of bilateral idiopathic trigeminal neuralgia by radiofrequency thermocoagulation at different temperatures. *Medicine (Baltimore)* 2016; 95:e4274.
24. Yao P, Hong T, Zhu YQ, et al. Efficacy and safety of continuous radiofrequency thermocoagulation plus pulsed radiofrequency for treatment of V1 trigeminal neuralgia: A prospective cohort study. *Medicine* 2016; 95:e5247.
25. Zhao WX, Wang Q, He MW, Yang LQ, Wu BS, Ni JX. Radiofrequency thermocoagulation combined with pulsed radiofrequency helps relieve postoperative complications of trigeminal neuralgia. *Genet Mole Res* 2015; 14:7616-7623.
26. Luo F, Wang T, Shen Y, Meng L, Lu J, Ji N. High voltage pulsed radiofrequency for the treatment of refractory neuralgia of the infraorbital nerve: A prospective double-blinded randomized controlled study. *Pain Physician* 2017; 20:271-279.
27. Obermann M, Yoon MS, Ese D, et al. Impaired trigeminal nociceptive processing in patients with trigeminal neuralgia. *Neurology* 2007; 69:835-841.
28. Rodriguez E, Sakurai K, Xu J, et al. A craniofacial-specific monosynaptic circuit enables heightened affective pain. *Nat Neurosci* 2017; 20:1734-1743.
29. Khadilkar SV, Patil VA. Medical management of trigeminal neuralgia. *Neurol India* 2021; 69:S199-S205.
30. Fang L, Ying S, Tao W, Lan M, Xiaotong Y, Nan J. 3D CT-guided pulsed radiofrequency treatment for trigeminal neuralgia. *Pain Pract* 2014; 14:16-21.
31. Zhang C, Mei L, Xia M, Shen J, Huang B, Huang X. CT-guided radiofrequency treatment of trigeminal neuralgia at different temperatures through foramen rotundus. *Am J Transl Res* 2021; 13:3102-3110.
32. Meng Q, Zhang W, Yang Y, Zhou M, Li X. Cardiovascular responses during percutaneous radiofrequency thermocoagulation therapy in primary trigeminal neuralgia. *Journal Neurosurg Anesthesiol* 2008; 20:131-135.
33. Bhatjiwale M, Bhatjiwale M, Naik L D, Chopade P. Bi-modal radiofrequency treatment for coexisting neuralgia and neuropathy in adjacent divisions of the trigeminal nerve. *Int J Oral Maxillofac Surg* 2018; 47:1557-1560.
34. Yao PWZ, Hong T. Comparative observation of bilateral trigeminal neuralgia after radiofrequency thermocoagulation at different temperatures. *Chinese J Pain Med* 2017; 23:33-38.

Appendix 1. *Search strategy*

EMBASE

Session Results

'pulsed radiofrequency treatment'/exp OR 'radiofrequency ablation'/exp OR 'radiofrequency therapy'/exp AND 'random':ti,ab OR 'placebo':ti,ab OR 'double-blind':ti,ab AND 'neuralgia, trigeminal':ti,ab OR 'trigeminal 1,062 29 Nov 2021 neuralgias':ti,ab OR 'tic doloureux':ti,ab OR 'fothergill disease':ti,ab OR 'disease, fothergill':ti,ab OR 'trifacial neuralgia':ti,ab OR 'neuralgia, trifacial':ti,ab OR 'trifacial neuralgias':ti,ab OR 'tic douloureux':ti,ab OR 'epileptiform neuralgia':ti,ab OR 'epileptiform neuralgias':ti,ab OR 'neuralgia, epileptiform':ti,ab OR 'secondary trigeminal neuralgia':ti,ab OR 'neuralgia, secondary trigeminal':ti,ab OR 'secondary trigeminal neuralgias':ti,ab OR 'trigeminal neuralgia, secondary':ti,ab OR 'trigeminal
neuralgia, idiopathic':ti,ab OR 'idiopathic trigeminal neuralgia':ti,ab OR 'idiopathic trigeminal neuralgias':ti,ab OR 'neuralgia, idiopathic trigeminal':ti,ab OR 'trigeminus neuralgia'/exp

WEB OF SCIENCE

Session Results

TS=((TS=(Neuralgia, Trigeminal)) OR TS=(Trigeminal Neuralgias)) OR TS=(Tic Doloureux)) OR TS=(Fothergill Disease)) OR TS=(Disease, Fothergill)) OR TS=(Trifacial Neuralgia)) OR TS=(Neuralgia, Trifacial)) OR TS=(Trifacial Neuralgias)) OR TS=(Tic Douloureux)) OR TS=(Epileptiform Neuralgia)) OR TS=(Epileptiform Neuralgias)) OR TS=(Neuralgia, Epileptiform)) OR TS=(Secondary Trigeminal Neuralgia)) OR TS=(Neuralgia, Secondary Trigeminal)) OR TS=(Secondary Trigeminal Neuralgias)) OR TS=(Trigeminal Neuralgia, Secondary)) OR TS=(Trigeminal Neuralgia, Idiopathic)) OR TS=(Idiopathic Trigeminal Neuralgia)) OR TS=(Idiopathic Trigeminal Neuralgias)) OR TS=(Neuralgia, Idiopathic Trigeminal) OR TS=(Trigeminal Neuralgia) AND TS=(random* controlled trial OR random* OR placebo) AND ((TS=(Pulsed Radiofrequency Treatment)) OR TS=(Radiofrequency Ablation)) OR TS=(Radiofrequency Therapy)

PUBMED

Session Results

(("Pulsed Radiofrequency Treatment"[Mesh] OR "Radiofrequency Ablation"[Mesh] OR "Radiofrequency Therapy"[Mesh]) AND (randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract])) AND ((((((((((((((((((((Neuralgia, Trigeminal[Title/Abstract]) OR (Trigeminal Neuralgias[Title/Abstract])) OR (Tic Doloureux[Title/Abstract])) OR (Fothergill Disease[Title/Abstract])) OR (Disease, Fothergill[Title/Abstract])) OR (Trifacial Neuralgia[Title/Abstract])) OR (Neuralgia, Trifacial[Title/Abstract])) OR (Trifacial Neuralgias[Title/Abstract])) OR (Tic Douloureux[Title/Abstract])) OR (Epileptiform Neuralgia[Title/Abstract])) OR (Epileptiform Neuralgias[Title/Abstract])) OR
(Neuralgia, Epileptiform[Title/Abstract])) OR (Secondary Trigeminal Neuralgia[Title/Abstract])) OR (Neuralgia, Secondary Trigeminal[Title/Abstract])) OR (Secondary Trigeminal Neuralgias[Title/Abstract])) OR (Trigeminal Neuralgia, Secondary[Title/Abstract])) OR (Trigeminal Neuralgia, Idiopathic[Title/Abstract])) OR (Idiopathic Trigeminal Neuralgia[Title/Abstract])) OR (Idiopathic Trigeminal Neuralgias[Title/Abstract])) OR (Neuralgia, Idiopathic Trigeminal[Title/Abstract]))

Appendix Table 1. ***Sensitivity analysis of PCRF and CRF therapies in excellent pain relief for TN at 12-24 months: RR, 95% CI, and heterogeneity.***

Time	Exclusion of one by one	RR	95%CI	I^2
12 months	Ding, 2019	1.34	0.80, 2.24	81%
	Elawamy, 2017	1.18	1.01, 1.38	0%
	Li, 2012	1.53	0.78, 3.03	82%
	Yao, 2016	1.53	0.83, 2.83	74%
24 months	Ding, 2019	4.73	0.06, 378.08	90%
	Elawamy, 2017	1.37	1.09, 1.73	0%
	Yao, 2016	4.40	0.15, 131.78	84%